Redox signaling in the gastrointestinal tract

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Redox signaling regulates physiological self-renewal, proliferation, migration and differentiation in gastrointestinal epithelium by modulating Wnt/β-catenin and Notch signaling pathways mainly through NADPH oxidases (NOXs). Importantly, commensal bacteria contribute to intestine epithelial homeostasis through NOX1- and dual oxidase 2-derived reactive oxygen species (ROS). The loss of redox homeostasis is involved in the pathogenesis and development of a wide diversity of gastrointestinal disorders, such as Barrett's esophagus, peptic ulcer, inflammatory bowel disease, colorectal cancer, acute pancreatitis, and pancreatic cancer. The overproduction of superoxide anion together with inactivation of superoxide dismutase contribute to the pathogenesis of Barrett's esophagus and its transformation to adenocarcinoma. In Helicobacter pylori-induced peptic ulcer, oxidative stress derived from the leukocyte infiltrate and NOX1 aggravates mucosal damage, particularly in HspB+ strains that downregulate Nrf2. Progression of inflammatory bowel disease relies on the balance between pro-inflammatory redox-sensitive pathways, such as NLRP3 inflammasome and NF-kappaB, and the adaptive up-regulation of Mn superoxide dismutase and glutathione peroxidase 2. In colorectal cancer, redox signaling exhibits two Janus faces: On the one hand, NOX1 up-regulation and derived hydrogen peroxide enhance Wnt/β-catenin and Notch proliferating pathways; on the other hand, ROS may disrupt tumor progression through different pro-apoptotic mechanisms. Glutathione depletion, disulfide stress, mitochondrial ROS, and nitrosative stress contribute to the pathogenesis of acute pancreatitis. Mitochondrial ROS also cooperates with mutant KRAS to trigger acinar-to-ductal metaplasia and progression to pancreatic adenocarcinoma. Therefore, redox signaling plays a fundamental role in the physiology and pathophysiology of gastrointestinal tract.